4-1-98 Filed

PCT (9-25-97)

08721447 9-27-96

```
Trying 01083...Open

PLEASE ENTER HOST PORT ID:
PLEASE ENTER HOST PORT ID:x
LOGINID:d160amd
PASSWORD:
 * * * * * * RECONNECTED TO U.S. Patent & Trademark Office * * * * * *
SESSION RESUMED IN FILE 'USPAT' AT 15:26:01 ON 04 OCT 1999
FILE 'USPAT' ENTERED AT 15:26:01 ON 04 OCT 1999
=> s clot (10N) inhib?

          5851 CLOT
        279953 INHIB?
L9         458 CLOT (10A) INHIB?

=> s mutein? or mutant? or mtat?

           760 MUTEIN?
         15049 MUTANT?
             5 MTAT?
L10      15385 MUTEIN? OR MUTANT? OR MTAT?

=> d his


     (FILE 'USPAT' ENTERED AT 15:10:02 ON 04 OCT 1999)
L1       105330 S CLOT?
L2       279849 S INHIBIT?
L3          756 S LI (P) L2
L4        22971 S MUTAT? OR MUTANT? OR MUTEIN?
L5         4194 S L4 (P) L2
L6           19 S L4 (P) L3
L7         1458 S L1 (10N) L2
L8           26 S L4 (P) L7
L9          458 S CLOT (10N) INHIB?
L10       15385 S MUTEIN? OR MUTANT? OR MTAT?

=> display 18 1-26 kwic abs cit

'ABS' IS NOT A VALID FORMAT FOR FILE 'USPAT'
ENTER DISPLAY FORMAT (CIT):cit


1.  5,916,763, Jun. 29, 1999, Promoter for VEGF receptor; Lewis T.
Williams, et al., 435/69.1, 70.1, 320.1, 325, 366, 455, 471; 536/24.1
[IMAGE AVAILABLE]

2.  5,882,941, Mar. 16, 1999, Programmable genotoxic agents and uses
therefor; John M. Essigmann, et al., 435/440; 530/350; 536/23.1, 23.5,
23.72; 552/502 [IMAGE AVAILABLE]

3.  5,880,256, Mar. 9, 1999, Factor VIIa inhibitors from Kunitz domain
proteins; Mark S. Dennis, et al., 530/324; 435/69.2; 530/300; 930/250
[IMAGE AVAILABLE]

4.  5,863,893, Jan. 26, 1999, Factor VIIa inhibitors from kunitz domain
proteins; Mark S. Dennis, et al., 514/12; 435/226; 514/822; 930/250
[IMAGE AVAILABLE]

5.  5,834,244, Nov. 10, 1998, Factor VIIa inhibitors from Kunitz domain
```

proteins; Mark S. Dennis, et al., 435/69.2, 252.3, 320.1, 325; 536/23.5; 930/250 [IMAGE AVAILABLE]

6. 5,831,031, Nov. 3, 1998, Antibodies that bind to .alpha.2-antiplasmin crosslinked to fibrin which do not inhibit plasma .alpha.2-antiplasmin; Guy L. Reed, et al., 530/388.1; 424/130.1, 141.1, 158.1; 530/387.1, 388.25 [IMAGE AVAILABLE]

7. 5,827,672, Oct. 27, 1998, Human monocyte elastase inhibitor antibodies; Eileen Remold-O'Donnell, 435/7.92, 7.1; 530/387.9, 388.15, 388.26 [IMAGE AVAILABLE]

8. 5,824,639, Oct. 20, 1998, Modified factor VII anticoagulant proteins; Kathleen L. Berkner, 514/12; 424/94.64; 435/212, 226; 530/384 [IMAGE AVAILABLE]

9. 5,773,601, Jun. 30, 1998, Inverted chimeric and hybrid oligonucleotides; Sudhir Agrawal, 536/24.5 [IMAGE AVAILABLE]

10. 5,773,228, Jun. 30, 1998, Activation-dependent protein expressed on the surface of activated platelets and antibodies thereto; Guy L. Reed, et al., 435/7.21; 424/1.49, 9.34, 9.4; 435/7.24, 86, 87; 530/388.7, 389.6 [IMAGE AVAILABLE]

11. 5,766,869, Jun. 16, 1998, Factor V ratio blood test for susceptibility to thromboembolism; Yale S. Arkel, et al., 435/13; 424/529, 530; 435/4, 23, 24, 214, 975; 436/63, 71; 530/380, 381 [IMAGE AVAILABLE]

12. 5,714,320, Feb. 3, 1998, Rolling circle synthesis of oligonucleotides and amplification of select randomized circular oligonucleotides; Eric T. Kool, 435/6, 5, 91.1, 91.2; 536/23.1, 24.3, 24.32, 24.33, 24.5 [IMAGE AVAILABLE]

13. 5,663,299, Sep. 2, 1997, Human monocyte elastase inhibitor; Eileen Remold-O'Donnell, 530/350; 435/218 [IMAGE AVAILABLE]

14. 5,652,356, Jul. 29, 1997, Inverted chimeric and hybrid oligonucleotides; Sudhir Agrawal, 536/24.5, 25.3 [IMAGE AVAILABLE]

15. 5,637,492, Jun. 10, 1997, Activatable fibrinolytic and anti-thrombotic proteins; Keith Dawson, et al., 435/217; 424/94.64; 435/212 [IMAGE AVAILABLE]

16. 5,626,841, May 6, 1997, Use of intra-platelet urokinase-type plasminogen activators for long-term inhibition of thrombosis; Victor Gurewich, 424/94.63, 94.64; 435/215, 226 [IMAGE AVAILABLE]

17. 5,620,688, Apr. 15, 1997, Methods of inhibiting the activation of Factor XIII; Guy L. Reed, et al., 424/145.1, 94.63, 94.64, 130.1, 139.1, 141.1, 146.1, 158.1 [IMAGE AVAILABLE]

18. 5,589,173, Dec. 31, 1996, Method and therapeutic compositions for the treatment of myocardial infarction; Donogh P. O'Brien, et al., 424/145.1, 158.1; 514/2, 4, 8; 530/381 [IMAGE AVAILABLE]

19. 5,582,862, Dec. 10, 1996, Antibodies that bind to .alpha.2-antiplasmin crosslinked to fibrin which do not inhibit plasma .alpha.2-antiplasmin; Guy L. Reed, et al., 424/145.1, 94.63, 94.64, 141.1; 530/388.25, 388.26 [IMAGE AVAILABLE]

20. 5,510,248, Apr. 23, 1996, Stable recombinant meizothrombin-like polypeptides; Helene C. F. Cote, et al., 435/69.6, 320.1, 352, 359, 364, 365, 369, 370; 536/23.2, 23.5 [IMAGE AVAILABLE]

21. 5,446,132, Aug. 29, 1995, Thrombin-activated platelet protein-2

(TAPP-2); Guy L. Reed, et al., 530/380; 435/7.2; 436/501; 530/350 [IMAGE AVAILABLE]

22. 5,372,812, Dec. 13, 1994, Composition and method for acceleration of clot lysis; Guy L. Reed, et al., 424/145.1, 94.63, 94.64; 530/388.25, 388.26 [IMAGE AVAILABLE]

23. 5,370,991, Dec. 6, 1994, Cloned gene encoding human monocyte elastase inhibitor; Eileen Remold-O'Donnell, 435/6; 536/23.2, 24.3, 24.31 [IMAGE AVAILABLE]

24. 5,288,629, Feb. 22, 1994, DNA sequence encoding Factor VII with an amino acid substitution at Avg-152; Kathleen L. Berkner, 435/352; 536/23.1 [IMAGE AVAILABLE]

25. 5,275,812, Jan. 4, 1994, Method of treatment for myocardial infarction; Herman K. Gold, et al., 424/145.1, 94.63; 530/388.25 [IMAGE AVAILABLE]

26. 4,711,848, Dec. 8, 1987, Site specific mutagenesis in alpha-1-antitrypsin; Margaret Y. Insley, et al., 435/69.2, 91.4, 91.41, 483; 536/23.1, 23.2; 930/250, DIG.530 [IMAGE AVAILABLE]

=> display l8 1-26 kwic

US PAT NO: 5,916,763 [IMAGE AVAILABLE] L8: 1 of 26

DETDESC:

DETD(58)

Thus . . . and the like. The proteins and polypeptides that may be expressed include cellular adhesion molecules, cytokines, hormones, growth factors, enzymes, **clotting** factors, apolipoproteins, receptors, drugs, **inhibitors** of intra- and extra-cellular processes, antigens and oncogenes. Specific examples include TNF.alpha., IL-2, granulocyte macrophage colony stimulating factor (GM-CSF), insulin like growth factor, tissue plasminogen activator, **mutant** VEGF receptors and the like. Thus, this invention provides methods of selective targeting and expression of such antitumor agents such. . . and prevent VEGF receptor expression, thus preventing tumor angiogenesis and tumor growth. Alternatively, endothelial specific expression of soluble VEGF receptor **mutants** capable of binding VEGF but incapable of stimulating endothelial cell mitogenesis such as those described in WO 94/21679 provides a. . .

US PAT NO: 5,882,941 [IMAGE AVAILABLE] L8: 2 of 26

DETDESC:

DETD(36)

The . . . that binds with high affinity to the extracellular protein thrombin (Bock et al. (1992), 355 Nature 564-566), and can even **inhibit** thrombin catalyzed blood **clot** formation. High affinity aptamers can be generated even against proteins for which there is little or no structural or ligand-recognition. . . like. A preferred aptamer binds to the nuclear phosphoprotein p53. A particularly preferred aptamer binds to a region of tumor-associated **mutant** p53 that is cryptic in wildtype p53, such as the PAb240 epitope (Gannon et al. (1990) 9 EMBO J. 1595-1602;. . . the PAb240 epitope has been prepared. Heterobifunctional compounds comprising an aptamer amplified from this pool and thus programmed to bind **mutant** p53 can be assessed for biomolecular and in vitro function through appropriate adaption of the techniques and guidelines set forth. . .

US PAT NO: 5,880,256 [IMAGE AVAILABLE] L8: 3 of 26

DETDESC:

DETD(159)

Samples . . . in the APTT assay. Rabbit Thromboplastin with Ca++was used for the PT assays; the rabbit thromboplastin was diluted two-fold. All **mutant inhibitors** tested prolonged **clotting** by at least one fold. TF7I-C showed the greatest **inhibition** of the surface mediated contact activation pathway, as measured by the activated partial thromboplastin time assay. A greater than 10. . .

DETDESC:

DETD(162)

Compared to the saline control, Heparin and the **mutant** APPI **inhibitors** TF7I-C and IV-49C significantly prolonged patency and reduced **clot** size for the time periods studied. For both TF7I-C and IV-49C the percentage of animals that remained patent for greater. . .

US PAT NO: 5,863,893 [IMAGE AVAILABLE] L8: 4 of 26

DETDESC:

DETD(156)

Samples . . . the APTT assay. Rabbit Thromboplastin with Ca++ was used for the PT assays; the rabbit thromboplastin was diluted two-fold. All **mutant inhibitors** tested prolonged **clotting** by at least one fold. TF7I-C showed the greatest **inhibition** of the surface mediated contact activation pathway, as measured by the activated partial thromboplastin time assay. A greater than 10. . .

DETDESC:

DETD(159)

Compared to the saline control, Heparin and the **mutant** APPI **inhibitors** TF7I-C and IV-49C significantly prolonged patency and reduced **clot** size for the time periods studied. For both TF7I-C and IV-49C the percentage of animals that remained patent for greater. . .

US PAT NO: 5,834,244 [IMAGE AVAILABLE] L8: 5 of 26

DETDESC:

DETD(158)

Samples . . . the APTT assay. Rabbit Thromboplastin with Ca++ was used for the PT assays; the rabbit thromboplastin was diluted two-fold. All **mutant inhibitors** tested prolonged **clotting** by at least one fold. TF7I-C showed the greatest **inhibition** of the surface mediated contact activation pathway, as measured by the activated partial thromboplastin time assay. A greater than 10. . .

DETDESC:

DETD(160)

Compared to the saline control, Heparin and the **mutant** APPI **inhibitors** TF7I-C and IV-49C significantly prolonged patency and reduced **clot** size for the time periods studied. For both TF7I-C and IV-49C the percentage of animals that remained patent for greater. . .

US PAT NO: 5,831,031 [IMAGE AVAILABLE] L8: 6 of 26

DETDESC:

DETD(10)

The term "thrombolytic agent" is meant to refer to any agent capable of either dissolving a fibrin-platelet **clot**, or **inhibiting** the formation of such a **clot**. Examples of thrombolytic agents include streptokinase, prourokinase, urokinase, and tissue-type plasminogen activator. Use of t-PA for these purposes is especially. . . may be employed, it is preferable to employ recombinant t-PA. The invention may additionally employ hybrids, physiologically active fragments or **mutant** forms of the above thrombolytic agents. The term "tissue-type plasminogen activator" as used herein is intended to include such hybrids, fragments and **mutants**, as well as both naturally derived and recombinantly derived tissue-type plasminogen activator.

US PAT NO: 5,827,672 [IMAGE AVAILABLE] L8: 7 of 26

DETDESC:

DETD(195)

By . . . so as to alter the inhibitory properties of human EI and render the variant molecule useful in other applications. A **mutant** human EI recombinant molecule with Arg substituted in P1 position with or without additional substitutions can have greatly reduced elastase inhibitory activity and can function instead as an **inhibitor** of thrombin, as for example, an anti-**clotting** agent. Alternatively, recombinant human EI variants with P1 Arg can function to inhibit plasminogen activator or C1-esterase and function in. . .

US PAT NO: 5,824,639 [IMAGE AVAILABLE] L8: 8 of 26

DETDESC:

DETD(48)

The ability of the **mutant** Factor VII (R152E) to compete with wild-type Factor VII for tissue factor and **inhibit** its **clotting** activity was assessed in a one-step **clotting** assay in the presence of limiting amounts of tissue factor (thromboplastin). If the two proteins reacted similarly with the Factor VII co-factor, tissue factor, R152E should **inhibit** the **clotting** activity of wild-type Factor VII.

US PAT NO: 5,773,601 [IMAGE AVAILABLE] L8: 9 of 26

SUMMARY:

BSUM(18)

In . . . or eukaryotic pathogen, or inappropriate expression of a host cellular gene. Inappropriate host cellular gene expression includes expression of a **mutant** allele of a cellular gene, or underexpression or overexpression of a normal allele of a cellular gene, such that disease. . . administered, one or more measurement is taken of biological effects selected from the group consisting of complement activation, mitogenesis and **inhibition** of thrombin **clot** formation.

DETDESC:

DETD(11)

In . . . or eukaryotic pathogen, or inappropriate expression of a host cellular gene. Inappropriate host cellular gene expression includes expression of a **mutant** allele of a cellular gene, or underexpression or overexpression of a normal allele of a cellular gene, such that disease. . . . administered, one or more measurement is taken of biological effects selected from the group consisting of complement activation, mitogenesis and **inhibition** of thrombin **clot** formation.

US PAT NO: 5,773,228 [IMAGE AVAILABLE] L8: 10 of 26

DETDESC:

DETD(20)

In . . . therapeutic or thrombolytic agents. The term "thrombolytic agent" is meant to refer to any agent capable of dissolving a fibrin-platelet **clot**, or **inhibiting** the formation of such a **clot**. Examples of thrombolytic agents include streptokinase, staphylokinase, prourokinase, urokinase, and tissue-type plasminogen activator. Natural activators or recombinant activators may be utilized. The invention may additionally employ hybrids, physiologically active fragments, **mutant** or chimeric forms of the above thrombolytic agents including single chain urokinase plasminogen activator (SCU-PA) and active fragments thereof. The term "plasminogen activator" as used herein is intended to include such hybrids, fragments and **mutants** as well as both naturally derived and recombinantly derived plasminogen activators. See, for example, Stump et al., J. Biol. Chem.. . .

US PAT NO: 5,766,869 [IMAGE AVAILABLE] L8: 11 of 26

SUMMARY:

BSUM(10)

Dahlback . . . of APC in the clotting sample. This assay is referred to as the APCR assay. The incidence of the FVL **mutation** in patients with a positive result of the APCR test was reported to be 94% among the tested population of. . . Because of the lack of a complete correlation between this APCR screening clotting test of APC resistance and the FVL **mutation**, it was postulated that there may be other mechanisms for APC resistance. Reports of the **clotting** assay being effected by the presence of lupus **inhibitor** (LI) antibodies, with resultant ratios indicating APC resistance, raised the issue of induced resistance due to the LI antibodies or. . . great deal to compensate for the above variables, making the test results more reflective of the presence of the FVL **mutation**.

US PAT NO: 5,714,320 [IMAGE AVAILABLE] L8: 12 of 26

DETDESC:

DETD(136)

A . . . of FK506 binding protein for activity as an immunosuppressant; binding of squalene synthase for a cholesterol lowering effect; binding of **mutated** p53 protein for an antitumor effect; binding of **mutated** ras protein for an antitumor effect; binding of the bcr-abl **mutant** protein for an antileukemic effect; binding of influenza coat proteins for an anti-influenza effect; binding opiate receptors for an analgesic. . . binding of resin to lower blood pressure; binding bcl-2 protein to induce apoptosis in cancer cells; binding of thrombin to **inhibit clotting**; and binding of NO-synthase to **inhibit** septic shock.

US PAT NO: 5,663,299 [IMAGE AVAILABLE] L8: 13 of 26

DETDESC:

DETD(192)

By . . . so as to alter the inhibitory properties of human EI and render the variant molecule useful in other applications. A **mutant** human EI recombinant molecule with Arg substituted in P1 position with or without additional substitutions can have greatly reduced elastase inhibitory activity and can function instead as an **inhibitor** of thrombin, as for example, an anti-**clotting** agent. Alternatively, recombinant human EI variants with P1 Arg can function to inhibit plasminogen activator or C1-esterase and function in. . .

US PAT NO: 5,652,356 [IMAGE AVAILABLE] L8: 14 of 26

SUMMARY:

BSUM(18)

In . . . or eukaryotic pathogen, or inappropriate expression of a host cellular gene. Inappropriate host cellular gene expression includes expression of a **mutant** allele of a cellular gene, or underexpression or overexpression of a normal allele of a cellular gene, such that disease. . . administered, one or more measurement is taken of biological effects selected from the group consisting of complement activation, mitogenesis and **inhibition** of thrombin **clot** formation.

DETDESC:

DETD(11)

In . . . or eukaryotic pathogen, or inappropriate expression of a host cellular gene. Inappropriate host cellular gene expression includes expression of a **mutant** allele of a cellular gene, or underexpression or overexpression of a normal allele of a cellular gene, such that disease. . . administered, one or more measurement is taken of biological effects selected from the group consisting of complement activation, mitogenesis and **inhibition** of thrombin **clot** formation.

US PAT NO: 5,637,492 [IMAGE AVAILABLE] L8: 15 of 26

SUMMARY:

BSUM(34)

The plasmin inhibitor alpha-2 antiplasmin is present in the blood and becomes incorporated into the fibrin matrix of blood **clots**. The role of this **inhibitor** is to restrict plasmin activity in the **clot** and in the circulation. For the highly clot selective analogues of plasminogen of the present invention it may be advantageous to introduce a **mutation** in the serine protease domain that interferes with plasmin inhibitor binding. This **mutation** could be in a position analogous to that shown to prevent inhibitor binding to tissue plasminogen activator (Madison, E. L.. . .

US PAT NO: 5,626,841 [IMAGE AVAILABLE] L8: 16 of 26

SUMMARY:

BSUM(26)

The invention also features a method of **inhibiting** the formation of platelet-mediated thrombi in a **clot**-free patient, by periodically,

e.g., once every 1 to 10 days, administering to the patient a bolus of an amount of purified pro-UK, e.g., pro-UK or thrombin-resistant **mutant** pro-UK, that inhibits the formation of occlusive thrombi without inducing a systemic effect in the patient, wherein the pro-UK becomes. . .

US PAT NO: 5,620,688 [IMAGE AVAILABLE] L8: 17 of 26

DETDESC:

DETD(98)

The term "thrombolytic agent" is meant to refer to any agent capable of either dissolving a fibrin-platelet **clot**, or **inhibiting** the formation of such a **clot**. Examples of thrombolytic agents include streptokinase, prourokinase, urokinase, and tissue-type plasminogen activator. Use of t-PA for these purposes is especially. . . t-PA may be employed, it is preferable to employ recombinant t-PA. The invention may additionally employ hybrids, physiologically active fragments, **mutant** or chimeric forms of the above thrombolytic agents including single chain urokinase plasminogen activator (scu-PA) and active fragments thereof. The term "tissue-type plasminogen activator" as used herein is intended to include such hybrids, fragments and **mutants**, as well as both naturally derived and recombinantly derived plasminogen activators.

US PAT NO: 5,589,173 [IMAGE AVAILABLE] L8: 18 of 26

DETDESC:

DETD(7)

The term "thrombolytic agent" is meant to refer to any agent capable of either dissolving a fibrin-platelet **clot**, or **inhibiting** the formation of such a **clot**. Examples of thrombolytic agents include streptokinase, prourokinase, urokinase, and tissue-type plasminogen activator ("t-PA"). Although natural t-PA (Collen, et al., EP. . . al., EP application publication no. 093,619, filed May 4, 1983). The invention may additionally employ hybrids, physiologically active fragments or **mutant** forms of the above thrombolytic agents. The term "tissue-type plasminogen activator" as used herein is intended to include such hybrids, fragments and **mutants**, as well as both naturally derived and recombinantly derived tissue-type plasminogen activator.

US PAT NO: 5,582,862 [IMAGE AVAILABLE] L8: 19 of 26

DETDESC:

DETD(10)

The term "thrombolytic agent" is meant to refer to any agent capable of either dissolving a fibrin-platelet **clot**, or **inhibiting** the formation of such a **clot**. Examples of thrombolytic agents include streptokinase, prourokinase, urokinase, and tissue-type plasminogen activator. Use of t-PA for these purposes is especially. . . may be employed, it is preferable to employ recombinant t-PA. The invention may additionally employ hybrids, physiologically active fragments or **mutant** forms of the above thrombolytic agents. The term "tissue-type plasminogen activator" as used herein is intended to include such hybrids, fragments and **mutants**, as well as both naturally derived and recombinantly derived tissue-type plasminogen activator.

US PAT NO: 5,510,248 [IMAGE AVAILABLE] L8: 20 of 26

DETDESC:

DETD(78)

The . . . amidolytic activities, which were approximately one half the activity obtained with plasma prothrombin treated with either activator. rhQM appeared to **inhibit** the reaction, leading to a **clotting** time longer then the one observed in the absence of protein (See buffer control). Although their level of .gamma.-carboxylation was probably not complete the **mutant** proteins can interact with the prothrombinase complex, thereby occupying sites, which decreases the rate of the reaction.

US PAT NO: 5,446,132 [IMAGE AVAILABLE] L8: 21 of 26

DETDESC:

DETD(20)

In . . . therapeutic or thrombolytic agents. The term "thrombolytic agent" is meant to refer to any agent capable of dissolving a fibrin-platelet **clot**, or **inhibiting** the formation of such a **clot**. Examples of thrombolytic agents include streptokinase, staphylokinase, prourokinase, urokinase, and tissue-type plasminogen activator. Natural activators or recombinant activators may be utilized. The invention may additionally employ hybrids, physiologically active fragments, **mutant** or chimeric forms of the above thrombolytic agents including single chain urokinase plasminogen activator (SCU-PA) and activefragments thereof. The term "plasminogen activator" as used herein is intended to include such hybrids, fragments and **mutants** as well as both naturally derived and recombinantly derived plasminogen activators. See, for example, Stump et al., J. Biol. Chem.. . .

US PAT NO: 5,372,812 [IMAGE AVAILABLE] L8: 22 of 26

DETDESC:

DETD(8)

The term "thrombolytic agent" is meant to refer to any agent capable of either dissolving a fibrin-platelet **clot**, or **inhibiting** the formation of such a **clot**. Examples of thrombolytic agents include streptokinase, prourokinase, urokinase, and tissue-type plasminogen activator. Use of t-PA for these purposes is especially. . . may be employed, it is preferable to employ recombinant t-PA. The invention may additionally employ hybrids, physiologically active fragments or **mutant** forms of the above thrombolytic agents. The term "tissue-type plasminogen activator" as used herein is intended to include such hybrids, fragments and **mutants**, as well as both naturally derived and recombinantly derived tissue-type plasminogen activator.

US PAT NO: 5,370,991 [IMAGE AVAILABLE] L8: 23 of 26

DETDESC:

DETD(116)

By . . . as to completely alter the inhibitory properties of human EI and render the variant molecule useful in other applications. A **mutant** human EI recombinant molecule with Arg substituted in P1 position with or without additional substitutions can have greatly reduced elastase inhibitory activity and can function instead as an **inhibitor** of thrombin, as for example, an anti-**clotting** agent. Alternatively, recombinant human EI variants with P1 Arg can function to inhibit plasminogen activator of C1-esterase and function in. . .

US PAT NO: 5,288,629 [IMAGE AVAILABLE] L8: 24 of 26

DETDESC:

DETD(48)

The ability of the **mutant** Factor VII (R152E) to compete with wild-type Factor VII for tissue factor and **inhibit** its **clotting** activity was assessed in a one-step **clotting** assay in the presence of limiting amounts of tissue factor (thromboplastin). If the two proteins reacted similarly with the Factor VII co-factor, tissue factor, R152E should **inhibit** the **clotting** activity of wild-type Factor VII.

US PAT NO: 5,275,812 [IMAGE AVAILABLE] L8: 25 of 26

SUMMARY:

BSUM(38)

The term "thrombolytic agent" is meant to refer to any agent capable of either dissolving a fibrin-platelet **clot**, or **inhibiting** the formation of such a **clot**. Examples of thrombolytic agents include streptokinase, prourokinase, urokinase, and tissue-type plasminogen activator. Although natural t-PA may be employed, it is preferable to employ recombinant t-PA. The invention may additionally employ hybrids, physiologically active fragments or **mutant** forms of the above thrombolytic agents. The term "tissue-type plasminogen activator" as used herein is intended to include such hybrids, fragments and **mutants**, as well as both naturally derived and recombinantly derived tissue-type plasminogen activator.

US PAT NO: 4,711,848 [IMAGE AVAILABLE] L8: 26 of 26

SUMMARY:

BSUM(2)

Alpha-1-antitrypsin . . . (1982). Owen et al. (New Eng. J. Med. 309: 694-698, 1983) describe a condition in which a patient produced a **mutant** form of alpha-1-antitrypsin having an arginine substituted for the methionine at amino acid position 358. As the result of a single **mutation** in the gene sequence (ATG to AGG), the alpha-1-antitrypsin had been converted from its normal function as an elastase inhibitor. . . . Carroll et al., ibid). These findings indicate that an altered form of AT could be clinically important for use in **inhibiting** blood **clotting**, as for example, in the treatment of disseminated intravascular coagulation.

DETDESC:

DETD(54)

In addition to the above-described uses of the **mutant** forms of AT, the protein comprising the methionine to arginine **mutation** at amino acid 358 may be used for **inhibition** of blood **clotting**, for example, in treating disseminated intravascular coagulation.

For 09/053,671

L10 ANSWER 1 OF 15 MEDLINE
ACCESSION NUMBER: 1999211940 MEDLINE
DOCUMENT NUMBER: 99211940
TITLE: Cleavage of factor V at Arg 506 by activated protein C and the expression of anticoagulant activity of factor V.
AUTHOR: Thorelli E; Kaufman R J; Dahlback B
CORPORATE SOURCE: Department of Clinical Chemistry, Lund University, University Hospital Malmo, Sweden.
SOURCE: BLOOD, (1999 Apr 15) 93 (8) 2552-8.
Journal code: A8G. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199907
ENTRY WEEK: 19990702
AB Activated protein C (APC) **inhibits** coagulation by cleaving and inactivating procoagulant factor Va (FVa) and factor VIIIa (FVIIIa). FV, in addition to being the precursor of FVa, has anticoagulant properties; functioning in synergy with protein S as a cofactor of APC in the **inhibition** of the FVIIIa-**factor IXa** (FIXa) complex. FV:Q506 isolated from an individual homozygous for APC-resistance is less efficient as an APC-cofactor than normal FV (FV:R506). To investigate the importance of the three APC cleavage sites in FV (Arg-306, Arg-506, and Arg-679) for expression of its APC-cofactor activity, four recombinant FV **mutants** (FV:Q306, FV:Q306/Q506, FV:Q506, and FV:Q679) were tested. FV **mutants** with Gln (Q) at position 506 instead of Arg (R) were found to be poor APC-cofactors, whereas Arg to Gln **mutations** at positions 306 or 679 had no negative effect on the APC-cofactor activity of FV. The loss of APC-cofactor activity as a result of the Arg-506 to Gln **mutation** suggested that APC-cleavage at Arg-506 in FV is important for the ability of FV to function as an APC-cofactor. Using Western blotting, it was shown that both wild-type FV and mutant FV was cleaved by APC during the FVIIIa **inhibition**. At optimum concentrations of wild-type FV (11 nmol/L) and protein S (100 nmol/L), FVIIIa was found to be highly sensitive to APC with maximum **inhibition** occurring at less than 1 nmol/L APC. FV:Q506 was inactive as an APC-cofactor at APC-concentrations </= 1 nmol/L and only partially active at higher APC concentrations. Our results show that increased expression of FV anticoagulant activity correlates with APC-mediated cleavage at Arg-506 in FV, but not with cleavage at Arg-306 nor at Arg-679.

L10 ANSWER 2 OF 15 MEDLINE
ACCESSION NUMBER: 1998102434 MEDLINE
DOCUMENT NUMBER: 98102434
TITLE: The molecular basis for cross-reacting material-positive hemophilia A due to missense mutations within the A2-domain of factor VIII.
AUTHOR: Amano K; Sarkar R; Pemberton S; Kemball-Cook G; Kazazian H H Jr; Kaufman R J
CORPORATE SOURCE: Howard Hughes Medical Institute, Ann Arbor, MI, USA.
CONTRACT NUMBER: HL53777 (NHLBI)

HL52173 (NHLBI)
SOURCE: BLOOD, (1998 Jan 15) 91 (2) 538-48.
Journal code: A8G. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199804

AB Factor VIII (FVIII) is the protein defective in the bleeding disorder hemophilia A. Approximately 5% of hemophilia A patients have normal amounts of a dysfunctional FVIII protein and are termed cross-reacting material (CRM)-positive. The majority of genetic alterations that result in CRM-positive hemophilia A are missense **mutations** within the A2-domain. To determine the mechanistic basis of the genetic defects within the A2-domain for FVIII function we constructed six **mutations** within the FVIII cDNA that were previously found in five CRM-positive hemophilia A patients (R527W, S558F, I566T, V634A, and V634M) and one CRM-reduced hemophilia A patient (DeltaF652/3). The specific activity for each mutant secreted into the conditioned medium from transiently transfected COS-1 cells correlated with published data for the patients plasma-derived FVIII, confirming the basis of the genetic defect. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis analysis of immunoprecipitated FVIII protein radiolabeled in COS-1 cells showed that all CRM-positive mutant proteins were synthesized and secreted into the medium at rates similar to wild-type FVIII. The majority of the DeltaF652/3 mutant was defective in secretion and was degraded within the cell. All mutant FVIII proteins were susceptible to thrombin cleavage, and the A2-domain fragment from the I566T mutant had a reduced mobility because of use of an introduced potential N-linked glycosylation site that was confirmed by N-glycanase digestion. To evaluate interaction of FVIII with **factor IXa**, we performed an **inhibition** assay using a synthetic peptide corresponding to FVIII residues 558 to 565, previously shown to be a **factor IXa** interaction site. The concentration of peptide required for 50% **inhibition** of FVIII activity (IC50) was reduced for the I566T (800 mumol/L) and the S558F (960 mumol/L) **mutants** compared with wild-type FVIII (> 2,000 mumol/L). N-glycanase digestion increased I566T mutant FVIII activity and increased its IC50 for the peptide (1,400 mumol/L). In comparison to S558F, a more conservative mutant (S558A) had a sixfold increased specific activity that also correlated with an increased IC50 for the peptide. These results provided support that the defects in the I566T and S558F FVIII molecules are caused by steric hindrance for interaction with **factor IXa**.

L10 ANSWER 3 OF 15 MEDLINE
ACCESSION NUMBER: 1998079048 MEDLINE
DOCUMENT NUMBER: 98079048
TITLE: Blood coagulation factor IX residues Glu78 and Arg94 provide a link between both epidermal growth factor-like domains that is crucial in the interaction with factor VIII light chain.
AUTHOR: Christophe O D; Lenting P J; Kolkman J A; Brownlee G G; Mertens K
CORPORATE SOURCE: Department of Plasma Protein Technology, Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, The Netherlands.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Jan 2) 273 (1) 222-7.

Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199804
ENTRY WEEK: 19980401
AB Recently, we established that **mutations** at calcium-binding sites within the first epidermal growth factor (EGF)-like domain of activated factor IX affect its interaction with factor VIIIa (Lenting, P. J., Christophe, O. D., ter Maat, H., Rees, D. J. G., and Mertens, K. (1996) J. Biol. Chem. 271, 25332-25337). In the present study, we have investigated the functional role of residue Glu78, which is not involved in calcium binding. Glu78 is also located in the first EGF-like domain and, when **mutated** to Lys, is associated with severe hemophilia B. Because Glu78 is conserved in related vitamin K-dependent proteins, it is difficult to understand how a **mutation** at this position is associated with factor IX-specific function. In this study, we addressed the hypothesis that Glu78 exerts its biological activity by interacting with another residue. One candidate was found to be the second EGF-like domain residue, Arg94, which is also associated with severe hemophilia B when **mutated**. We constructed a series of **mutants** that included **mutations** at position 78 alone (Glu78 to Lys/Glu78 to Asp) or at both positions 78 and 94 (Glu78 to Lys and Arg94 to Asp). The functional parameters of immunopurified and activated **mutants** were compared with normal activated factor IX. **Mutants** were indistinguishable from normal **factor IXa** in cleaving the synthetic substrate CH3SO2-Leu-Gly-Arg-p-nitroanilide or activating factor X in the absence of factor VIIIa. In contrast, in the presence of factor VIIIa, **factor IXa** Glu78 to Asp and **factor IXa** Glu78 to Lys/Arg94 to Asp were stimulated to the same extent as normal **factor IXa**, whereas **factor IXa** Glu78 to Lys was markedly less stimulated (140-fold versus 2,000-fold). This suggests that residues 78 and 94 should carry an opposite charge for a normal interaction of **factor IXa** to factor VIIIa. This hypothesis was confirmed in **inhibition** studies employing synthetic peptides comprising the **factor IXa**-binding motifs of factor VIII heavy (Ser558-Gln565) or light chain (Glu1811-Lys1818) and in direct binding studies. We propose that residues 78 and 94 link both EGF-like domains and thereby maintain the integrity of the factor VIII light chain binding site.

L10 ANSWER 4 OF 15 MEDLINE
ACCESSION NUMBER: 1998004487 MEDLINE
DOCUMENT NUMBER: 98004487
TITLE: Characterization of a genetically engineered inactivation-resistant coagulation factor VIIIa.
AUTHOR: Pipe S W; Kaufman R J
CORPORATE SOURCE: Department of Pediatrics, University of Michigan Medical Center, Ann Arbor, MI 48109, USA.
CONTRACT NUMBER: HL52173 (NHLBI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 Oct 28) 94 (22) 11851-6. Journal code: PV3. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199802
ENTRY WEEK: 19980204
AB Individuals with hemophilia A require frequent infusion of preparations of

coagulation factor VIII. The activity of factor VIII (FVIII) as a cofactor for **factor IXa** in the coagulation cascade is limited by its instability after activation by thrombin. Activation of FVIII occurs through proteolytic cleavage and generates an unstable FVIII heterotrimer that is subject to rapid dissociation of its subunits. In addition, further proteolytic cleavage by thrombin, factor Xa, **factor IXa**, and activated protein C can lead to inactivation. We have engineered and characterized a FVIII protein, IR8, that has enhanced in vitro stability of FVIII activity due to resistance to subunit dissociation and proteolytic inactivation. FVIII was genetically engineered by deletion of residues 794-1689 so that the A2 domain is covalently attached to the light chain. Missense **mutations** at thrombin and activated protein C inactivation cleavage sites provided resistance to proteolysis, resulting in a single-chain protein that has maximal activity after a single cleavage after arginine-372. The specific activity of partially purified protein produced in transfected COS-1 monkey cells was 5-fold higher than wild-type (WT) FVIII. Whereas WT FVIII was inactivated by thrombin after 10 min in vitro, IR8 still retained 38% of peak activity after 4 hr. Whereas binding of IR8 to von Willebrand factor (vWF) was reduced 10-fold compared with WT FVIII, in the presence of an anti-light chain antibody, ESH8, binding of IR8 to vWF increased 5-fold. These results demonstrate that residues 1690-2332 of FVIII are sufficient to support high-affinity vWF binding. Whereas ESH8 **inhibited** WT factor VIII activity, IR8 retained its activity in the presence of ESH8. We propose that resistance to A2 subunit dissociation abrogates **inhibition** by the ESH8 antibody. The stable FVIIIa described here provides the opportunity to study the activated form of this critical coagulation factor and demonstrates that proteins can be improved by rationale design through genetic engineering technology.

L10 ANSWER 5 OF 15 MEDLINE
ACCESSION NUMBER: 96411744 MEDLINE
DOCUMENT NUMBER: 96411744
TITLE: Ca2+ binding to the first epidermal growth factor-like domain of human blood coagulation factor IX promotes enzyme activity and factor VIII light chain binding.
AUTHOR: Lenting P J; Christophe O D; Maat H; Rees D J G; Mertens K
CORPORATE SOURCE: Department of Plasma Protein Technology, Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, 1066 CX Amsterdam, the Netherlands.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Oct 11) 271 (41) 25332-7.
Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199701
ENTRY WEEK: 19970104
AB Ca2+ binding to the first epidermal growth factor (EGF)-like domain of factor IX is known to be required for biological activity, but the mechanism by which Ca2+ contributes to factor IX function has remained unclear. We have studied recombinant factor IX **mutants** which lack Ca2+ binding to the first EGF-like domain, due to a replacement of Asp64 by Glu, Lys, or Val. The purified **mutants** (factors IX D64E, D64K, and D64V), were compared to plasma-derived and recombinant wild-type factor IX with regard to a number of metal-ion dependent functional parameters. In the presence of Mg2+, the activated **mutants** were indistinguishable from normal **factor IXa** in hydrolyzing the synthetic substrate CH3-SO2-Leu-Gly-Arg-p-nitroanilide. Replacing Mg2+ by Ca2+ further stimulated the activity of normal **factor IXa** but not of mutant **factor**

IXa. In factor VIII-independent factor X activation, **factor IXa** D64K and D64E displayed reduced catalytic activity compared to normal **factor IXa** (apparent kcat/Km approximately 1, 2, and 4 x 10(3) M-1 s-1, respectively). In the presence of factor VIIIa, factor X activation rates by normal and mutant **factor IXa** were stimulated by factor VIIIa to a different extent (approximately700- and 200-fold, respectively), indicating that Asp64 replacements affect the interaction with factor VIIIa. This possibility was addressed in **inhibition** studies employing synthetic peptides comprising the **factor IXa** -binding motifs of factor VIII heavy or light chains. Whereas the heavy chain peptide (Ser558-Gln565) **inhibited** factor VIII-dependent factor X activation by normal and mutant **factor IXa** with similar efficiency, the light chain peptide (Lys1804-Lys1818) **inhibited** normal **factor IXa** 2-3-fold more efficiently than did mutant **factor IXa**. This indicates that the reduced response to factor VIIIa may be due to impaired binding of mutant **factor IXa** to the factor VIII light chain. This was further explored in direct binding studies. In the presence of Mg2+, normal and mutant **factor IXa** were similar in binding to the factor VIII light chain. However, in the presence of Ca2+, **factor IXa mutants** were less efficient than normal **factor IXa**, which was illustrated by a 4-5-fold lower affinity than normal **factor IXa** for factor VIII light chain. Collectively, our data demonstrate that a number of **factor IXa** functions, including enzymatic activity and assembly into the **factor IXa-factor** VIIIa complex, are dependent on Ca2+ binding to the first EGF-like domain of factor IX.

L10 ANSWER 6 OF 15 MEDLINE
ACCESSION NUMBER: 96096732 MEDLINE
DOCUMENT NUMBER: 96096732
TITLE: Functional consequences of the Ser334-->Pro mutation in a human factor X variant (factor XMarseille).
AUTHOR: Bezeaud A; Miyata T; Helley D; Zeng Y Z; Kato H; Aillaud M F; Juhan-Vague I; Guillin M C
CORPORATE SOURCE: Laboratoire de Recherche sur l'Hemostase et la Thrombose, Faculte Xavier Bichat, Paris, France.
SOURCE: EUROPEAN JOURNAL OF BIOCHEMISTRY, (1995 Nov 15) 234 (1) 140-7.
Journal code: EMZ. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199604

AB A factor X molecular variant was identified in a 55-year-old woman at a routine preoperative coagulation screening. Plasma factor X antigen was normal, whereas factor X activity was decreased when factor X was activated by either the extrinsic pathway (21%), the intrinsic pathway (21%) or the factor X activator from Russell viper venom, RVV-X (26%). Factor XMarseille was isolated from plasma by immunoaffinity chromatography and compared with normal factor X purified by the same method. Activation of factor XMarseille by **factor IXa** or by RVV-X in a purified system showed that the rate of cleavage was decreased, whereas once produced, factor XaMarseille had a normal catalytic efficiency for either the peptide substrate S-2765 (D-Arg-Gly-Arg-NH-Np) or prothrombin. The rate of **inhibition** of factor XaMarseille by antithrombin III was also normal. Defective proteolysis of factor XMarseille by **factor IXa** or by RVV-X was the consequence of a threefold decrease in the kcat for the activation of factor XMarseille while the Km of RVV-X or **factor IXa** for factor X was normal. We have determined the molecular basis of the defect in the factor XMarseille gene by amplification of all eight exons, single-strand conformational polymorphism analysis of the

amplified exons and subsequent sequence analysis. The patient was homozygous for a T-->C **mutation** in exon VIII, resulting in the substitution of Ser334 by proline. From comparison of three-dimensional models of various serine proteases, it appears that Ser334 is located within a surface-exposed variable region of factor X. This observation suggests that the Ser334-->Pro **mutation** either is responsible for a misalignment of the active sites of specific factor X activators in close proximity to the cleavage site, or that the Ser-->Pro **mutation** alters the spatial orientation of the cleavage site by nonlocal modifications of factor X structure.

L10 ANSWER 7 OF 15 MEDLINE
ACCESSION NUMBER: 96003866 MEDLINE
DOCUMENT NUMBER: 96003866
TITLE: X-ray structure of clotting factor IXa: active site and module structure related to Xase activity and hemophilia B.
AUTHOR: Brandstetter H; Bauer M; Huber R; Lollar P; Bode W
CORPORATE SOURCE: Max-Planck-Institut fur Biochemie, Martinsried, Germany.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1995 Oct 10) 92 (21) 9796-800.

Journal code: PV3. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
OTHER SOURCE: GENBANK-U51135
ENTRY MONTH: 199601

AB Hereditary deficiency of **factor IXa** (fIXa), a key enzyme in blood coagulation, causes hemophilia B, a severe X chromosome-linked bleeding disorder afflicting 1 in 30,000 males; clinical studies have identified nearly 500 deleterious variants. The x-ray structure of porcine fIXa described here shows the atomic origins of the disease, while the spatial distribution of **mutation** sites suggests a structural model for factor X activation by phospholipid-bound fIXa and cofactor VIIIa. The 3.0-A-resolution diffraction data clearly show the structures of the serine proteinase module and the two preceding epidermal growth factor (EGF)-like modules; the N-terminal Gla module is partially disordered. The catalytic module, with covalent **inhibitor** D-Phe-1I-Pro-2I-Arg-3I chloromethyl ketone, most closely resembles fXa but differs significantly at several positions. Particularly noteworthy is the strained conformation of Glu-388, a residue strictly conserved in known fIXa sequences but conserved as Gly among other trypsin-like serine proteinases. Flexibility apparent in electron density together with modeling studies suggests that this may cause incomplete active site formation, even after zymogen, and hence the low catalytic activity of fIXa. The principal axes of the oblong EGF-like domains define an angle of 110 degrees, stabilized by a strictly conserved and fIX-specific interdomain salt bridge. The disorder of the Gla module, whose hydrophobic helix is apparent in electron density, can be attributed to the absence of calcium in the crystals; we have modeled the Gla module in its calcium form by using prothrombin fragment 1. The arched module arrangement agrees with fluorescence energy transfer experiments. Most hemophilic **mutation** sites of surface fIX residues occur on the concave surface of the bent molecule and suggest a plausible model for the membrane-bound ternary fIXa-FVIIIa-fX complex structure: fIXa and an equivalently arranged fX arch across an underlying fVIIIa subdomain from opposite sides; the stabilizing fVIIIa interactions force the catalytic modules together, completing fIXa active site formation and catalytic enhancement.

L10 ANSWER 8 OF 15 MEDLINE
ACCESSION NUMBER: 95357786 MEDLINE
DOCUMENT NUMBER: 95357786
TITLE: Studies on phospholipid antibodies, APC-resistance and associated mutation in the coagulation factor V gene.
AUTHOR: Bokarewa M I; Bremme K; Falk G; Sten-Linder M; Egberg N; Blomback M
CORPORATE SOURCE: Department of Laboratory Medicine/Blood Coagulation Research, Karolinska Institute, Stockholm, Sweden..
SOURCE: THROMBOSIS RESEARCH, (1995 May 1) 78 (3) 193-200. Journal code: VRN. ISSN: 0049-3848.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199511
AB The influence of antibodies against phospholipids (PLa) on APC response was investigated in 155 women with a history of thromboembolism and/or repeated foetal losses. PLa were determined as antibodies against cardiolipin (CLa) and phosphatidyl serine (PSa) and as lupus anticoagulant (LA) tested by dilute Russell's Viper Venom time and by the Textarin/Ecarin ratio. APC-response was studied by a clotting (aPTT-based) and by an amidolytic (**factor IXa**-X-based) assay. A reduced response to APC (APC-resistance) was found in 49% of 65 PLa-positive and in 13% of 90 PLa-negative samples (chi 2 = 23.9; p < 0.5 x 10(-4)). It was more common in the samples with LA, as compared to CLa+PSa positive (58% vs. 30%, not significant). The presence of the **mutation** causing Arg506-Gln substitution in coagulation factor V was investigated in 84 samples. The occurrence of the **mutation** in APC-resistant patients with CLa+PSa or with LA in one of the two assays was similar to those without PLa (84% and 100%, respectively). In the absence of APC resistance, the occurrence of the **mutation** was similar in the samples with and without PLa (14% vs. 11%). Samples with LA, determined by both tests used, comprised a special group where the frequency of the **mutation** in the APC resistant samples was significantly reduced (p < 0.01). In the latter samples, the pathogenic mechanism of APC resistance may be connected with the influence on phospholipid membranes.

L10 ANSWER 9 OF 15 MEDLINE
ACCESSION NUMBER: 95247757 MEDLINE
DOCUMENT NUMBER: 95247757
TITLE: Kinetic characterization of the proteinase binding defect in a reactive site variant of the serpin, antithrombin. Role of the P1' residue in transition-state stabilization of antithrombin-proteinase complex formation.
AUTHOR: Olson S T; Stephens A W; Hirs C H; Bock P E; Bjork I
CORPORATE SOURCE: Center for Molecular Biology of Oral Diseases, University of Illinois-Chicago, Chicago 60612, USA.
CONTRACT NUMBER: HL-39888 (NHLBI)
HL-02832 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Apr 28) 270 (17) 9717-24. Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199508
AB To elucidate the role of the P1' residue of the serpin, antithrombin (AT), in proteinase **inhibition**, the source of the functional defect in

a natural Ser-394-->Leu variant, AT-Denver, was investigated. AT-Denver **inhibited** thrombin, **Factor IXa**, plasmin, and Factor Xa with second order rate constants that were 430-, 120-, 40-, and 7-fold slower, respectively, than those of native AT, consistent with an altered specificity of the variant **inhibitor** for its target proteinases. AT-Denver **inhibited** thrombin and Factor Xa with nearly equimolar stoichiometries and formed SDS-stable complexes with these proteinases, indicating that the diminished **inhibitor** activity was not due to an enhanced turnover of the **inhibitor** as a substrate. Binding and kinetic studies showed that heparin binding to AT-Denver as well as heparin accelerations of AT-Denver-proteinase reactions were normal, consistent with the P1' **mutation** not affecting the heparin activation mechanism. Resolution of the two-step reaction of AT-Denver with thrombin revealed that the majority of the defective function was localized in the second reaction step and resulted from a 190-fold decreased rate constant for conversion of a noncovalent proteinase-**inhibitor** encounter complex to a stable, covalent complex. Little or no effects of the **mutation** on the binding constant for encounter complex formation or on the rate constant for stable complex dissociation were evident. These results support a role for the P1' residue of antithrombin in transition-state stabilization of a substrate-like attack of the proteinase on the **inhibitor** -reactive bond following the formation of a proteinase-**inhibitor** encounter complex but prior to the conformational change leading to the trapping of proteinase in a stable, covalent complex. Such a role indicates that the P1' residue does not contribute to thermodynamic stabilization of AT-proteinase complexes and instead favors a kinetic stabilization of these complexes by a suicide substrate reaction mechanism.

L10 ANSWER 10 OF 15 MEDLINE
ACCESSION NUMBER: 94362232 MEDLINE
DOCUMENT NUMBER: 94362232
TITLE: The role of amino-terminal residues of the heavy chain of factor IXa in the binding of its cofactor, factor VIIIa.
AUTHOR: Hamaguchi N; Bajaj S P; Smith K J; Stafford D W
CORPORATE SOURCE: Department of Biochemistry, Duke University Medical Center, Durham, NC..
CONTRACT NUMBER: RO1 HL38973 (NHLBI)
SOURCE: BLOOD, (1994 Sep 15) 84 (6) 1837-42. Journal code: A8G. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199412
AB The purpose of this study is to determine which residues of the **factor IXa** heavy chain are important for interaction with the cofactor of **factor IXa**, **factor** VIIIa. Because the monoclonal antibody (MoAb) FXC008 **inhibits** interaction between **factors IXa** and VIIIa, and because it also reacts with residues 181-310 of the **factor IXa** heavy chain, we used the computer-modelled structure of the **factor IXa** heavy chain to select charged surface residues likely to interact with FXC008 and/or factor VIIIa. We made **mutations** in the region of residues 181-310 of the heavy chain of factor IX, and replaced these amino acids individually with those located at the same position in factor X. The **mutated** factor IX retained complete clotting activity and thus interacted normally with factor VIIIa. Five mutant proteins (factor IXK214F, factor IXK228R, factor IXE240Q, factor IXK247V, and factor IXN260K) reacted with heavy chain-specific MoAbs FXC008 and A-5. Neither factor IXD276K nor factor IXR248H bound to FXC008.

Factor IXR252V had reduced affinity to FXC008. Our results suggest the following: (1) **factor IXa** residues 214, 228, 240, 247, 248, 252, 260, and 276 are not involved in specific interaction with factor VIIIa; and (2) the FXC008 and factor VIIIa binding sites may not share critical residues.

L10 ANSWER 11 OF 15 MEDLINE
ACCESSION NUMBER: 94308124 MEDLINE
DOCUMENT NUMBER: 94308124
TITLE: Factor V and protein S as synergistic cofactors to activated protein C in degradation of factor VIIIa.
AUTHOR: Shen L; Dahlback B
CORPORATE SOURCE: Department of Clinical Chemistry, University of Lund, Malmo General Hospital, Sweden..
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1994 Jul 22) 269 (29) 18735-8.
Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199410
AB Inherited resistance to activated protein C (APC) is a recently identified major cause of thrombosis. It is associated with a **mutation** in the factor V gene affecting one of the cleavage sites for APC. APC resistance was recently found to be corrected by factor V, suggesting that factor V may have anticoagulant properties as a cofactor to APC. To elucidate this further, we have studied the effect of factor V and protein S, which is a known cofactor to APC, on APC-mediated degradation of factor VIIIa in a purified system. The APC-mediated degradation of factor VIIIa was monitored by a factor X activation reaction using purified **factor IXa**, phospholipid, and calcium. In the presence of both factor V and protein S, APC was found to **inhibit** factor VIIIa activity efficiently. APC alone or together with factor V was ineffective, whereas APC in combination with protein S was less efficient than when factor V was also included in the reaction. Two monoclonal antibodies, one against protein S and the other directed toward factor V, were found to **inhibit** the APC cofactor activity of the factor V-protein S mixture. Factor Va did not express APC cofactor activity, and addition of excess factor Va over factor V did not **inhibit** the APC cofactor function of a factor V-protein S mixture. In conclusion, the results suggest that factor V and protein S work in synergy as phospholipid-bound cofactors to APC.

L10 ANSWER 12 OF 15 MEDLINE
ACCESSION NUMBER: 92163090 MEDLINE
DOCUMENT NUMBER: 92163090
TITLE: Hemophilia B caused by five different nondeletion mutations in the protease domain of factor IX.
AUTHOR: Ludwig M; Sabharwal A K; Brackmann H H; Olek K; Smith K J; Birktoft J J; Bajaj S P
CORPORATE SOURCE: Institute of Experimental Haematology and Blood Transfusion, Bonn, Germany.
CONTRACT NUMBER: HL36365 (NHLBI)
HL30572 (NHLBI)
HL07107 (NHLBI)
SOURCE: BLOOD, (1992 Mar 1) 79 (5) 1225-32.
Journal code: A8G. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199206

AB Factor IX is a multidomain protein and is the proenzyme of a serine protease, **factor IXa**, essential for hemostasis. In this report, we describe the molecular basis of hemophilia B (deficiency of factor IX activity) in five patients who have neither deletions nor rearrangements of the factor IX gene. By enzymatic amplification and sequencing of all exons and promoter regions, the following causative **mutation** in the protease domain of factor IX was identified in each patient: IXSchmallenberg: nucleotide 31,215G----T, Ser365Ile; IXVarel: nucleotide 31,214A----G, Ser365Gly; IXMechtal: nucleotide 31,211G----C, Asp364His; IXDreihacken: nucleotide 30,864G----A, Arg248Gln; and IXMonschau: nucleotide 30,855A----T, Glu245Val. In IXVarel, nucleotide 31,213T was also replaced by C, which results in a silent **mutation** (GAT----GAC) at Asp-364. Thus, this patient has a double base-pair substitution of TA to CG at nucleotides 31,213 and 31,214 but only a single amino acid change of Ser-365 to Gly. This patient also developed an antibody to factor IX during replacement therapy, which suggests that deletion of the factor IX gene is not necessary for development of the antibody in hemophilia B patients. The levels of plasma factor IX antigen in the patients ranged from 40% to 100% except for IXDreihacken (Arg248Gln), in which case it was approximately 4% of normal. The Ser365Gly and Ser365Ile **mutants** are nonfunctional because of lack of the active site serine residue. Mutant Asp364His is inactive because it cannot form the hydrogen bond between the carboxylate group of Asp-364 and the alpha-amino group of Val-181 generated after activation. As observed in other homologous serine proteases, this hydrogen bond is essential for maintaining the correct active site conformation in normal **factor IXa** (IXaN). Purified Arg248Gln had approximately 41% and Glu245Val had approximately 17% of the activity of normal factor IX (IXN) in a partial thromboplastin time (aPTT) assay. In immunodot blot experiments, the isolated Glu245Val mutant did and the Arg248Gln mutant did not bind to an anti-IXN monoclonal antibody that has been shown previously to **inhibit** the interaction of factor VIIIa with factor IXaN. We have recently shown that a high-affinity calcium binding site exists in the protease domain of IXN; among the proposed Ca(2+)-binding ligands is the carboxyl group of Glu-245. Further, a part of the epitope for the above antibody was shown to be contained in the 231 to 265 residue segment of factor IX.(ABSTRACT TRUNCATED AT 400 WORDS)

L10 ANSWER 13 OF 15 MEDLINE
ACCESSION NUMBER: 90293016 MEDLINE
DOCUMENT NUMBER: 90293016
TITLE: Mutations in hemophilia Bm occur at the Arg180-Val activation site or in the catalytic domain of factor IX.
AUTHOR: Bertina R M; van der Linden I K; Mannucci P M; Reinalda-Poot H H; Cupers R; Poort S R; Reitsma P H
CORPORATE SOURCE: Haemostasis and Thrombosis Research Unit, University Hospital, Leiden, The Netherlands.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1990 Jul 5) 265 (19) 10876-83.
Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199010

AB Hemophilia Bm is characterized by a strikingly prolonged plasma ox brain prothrombin time. In an attempt to find an explanation for this phenomenon

we have analyzed various aspects of the Bm variants factor IX Deventer, factor IX Milano, factor IX Novara, and factor IX Bergamo. Proteolytic cleavage by factor XIa was normal in two Bm variants, but absent at the Arg180-Val bond in the other two. In the latter variants Arg180 was replaced by either Trp or Gln, whereas Val181----Phe and Pro368----Thr replacements have occurred in the variants that were normally cleaved by factor XIa. In all four variants the Bm effect could be neutralized with a single monoclonal antibody against factor IX. Also, after treatment with factor XIa, none of the Bm variants reacted with antithrombin III (in contrast to normal **factor IXa**). Purified factor IX Deventer (one of the variants with a replacement of Arg181), either with or without pretreatment with factor XIa, was found to be a more effective competitive **inhibitor** of the factor VIIa-tissue factor-induced factor X activation than similarly treated normal factor IX. In addition, this **inhibitory** effect was much more pronounced when bovine tissue factor was used instead of human tissue factor. We propose that the normal activation of factor IX not only produces a conformational change around the active site serine that allows efficient substrate binding and catalysis, but that the same conformational change is instrumental in effectively dissociating **factor IXa** from the activating factor VIIa-tissue factor complex. Amino acid replacements that disrupt this conformational transition directly (e.g. Pro368----Thr near the catalytic center) or indirectly (**mutations** at the Arg180-Val activation site) therefore lead to a combination of 1) the loss of coagulant activity and 2) an **inhibitory** effect in the ox brain prothrombin time assay.

L10 ANSWER 14 OF 15 MEDLINE
ACCESSION NUMBER: 90153930 MEDLINE
DOCUMENT NUMBER: 90153930
TITLE: Experimental and theoretical evidence supporting the role of Gly363 in blood coagulation factor IXa (Gly193 in chymotrypsin) for proper activation of the proenzyme.
AUTHOR: Bajaj S P; Spitzer S G; Welsh W J; Warn-Cramer B J; Kasper C K; Birktoft J J
CORPORATE SOURCE: Department of Medicine, St. Louis University School of Medicine, Missouri 63104.
CONTRACT NUMBER: HL36365 (NHLBI)
HL30572 (NHLBI)
HL07050 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1990 Feb 15) 265 (5) 2956-61.
Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199005

AB Factor IX is the zymogen of the serine protease **factor IXa** involved in blood coagulation. In addition to a catalytic domain homologous to the chymotrypsin family, it has Ca2+, phospholipid, and factor VIIIa binding regions needed for full biologic activity. We isolated a nonfunctional factor IX protein designated factor IXEagle Rock (IXER) from a patient with hemophilia B. The variant protein is indistinguishable from normal factor IX (IXN) in its migration on sodium dodecyl sulfate-gel electrophoresis, isoelectric point in urea, carbohydrate content and distribution, number of gamma-carboxyglutamic acid residues, and beta-OH aspartic acid content, and in its binding to an anti-IXN monoclonal antibody which has been shown previously to **inhibit** the interaction of factor VIIIa with factor IXaN. Further, IXER is cleaved to yield a **factor IXa**-like molecule by factor XIa/Ca2+ at a rate similar to that observed for IXN. However, in

contrast to IXaN, IXaER does not bind to antithrombin-III (specific **inhibitor** of IXaN) and does not catalyze the activation of factor X (substrate) to factor Xa. To identify the **mutation** in IXER, all eight exons of IXN and IXER gene were amplified by the polymerase chain reaction technique and cloned. A single point **mutation** (G----T) which results in the replacement of Val for Gly363 in the catalytic domain of IXER was identified. Gly363 in **factor IXa** corresponds to the universally conserved Gly193 in the active site sequence of the chymotrypsin serine protease family. X-ray crystallographic data in the literature demonstrate a critical role of this Gly in stabilizing the active conformation of chymotrypsin/trypsin in two major ways: 1) in the formation of the substrate binding site; and 2) in the development of the oxyanion hole. Our computer structural data support a concept that the Gly363----Val change prevents the development of the active site conformation in **factor IXa** such that the substrate binding site and the oxyanion hole are not formed in the **mutated** enzyme.

L10 ANSWER 15 OF 15 MEDLINE
ACCESSION NUMBER: 90147571 MEDLINE
DOCUMENT NUMBER: 90147571
TITLE: Replacement of isoleucine-397 by threonine in the clotting proteinase **factor IXa** (Los Angeles and Long Beach variants) affects macromolecular catalysis but not L-tosylarginine methyl ester hydrolysis. Lack of correlation between the ox brain prothrombin time and the **mutation** site in the variant proteins.
AUTHOR: Spitzer S G; Warn-Cramer B J; Kasper C K; Bajaj S P
CORPORATE SOURCE: Department of Medicine, St. Louis University School of Medicine, MO 63104..
CONTRACT NUMBER: HL36365 (NHLBI)
HL30572 (NHLBI)
HL07050 (NHLBI)
+
SOURCE: BIOCHEMICAL JOURNAL, (1990 Jan 1) 265 (1) 219-25.
Journal code: 9YO. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199005

AB Previously, from the plasma of unrelated haemophilia-B patients, we isolated two non-functional Factor IX variants, namely Los Angeles (IXLA) and Long Beach (IXLB). Both variants could be cleaved to yield **Factor IXa**-like molecules, but were defective in catalysing the cleavage of Factor X (macromolecular substrate) and in binding to antithrombin III (macromolecular **inhibitor**). In the present study we have identified the **mutation** of IXLA by amplifying the exons (including flanking regions) as well as the 5' end of the gene by polymerase-chain-reaction (PCR) method and sequencing the amplified DNA by the dideoxy chain-termination method. Comparison of the normal IX and IXLA sequences revealed only one base substitution (T----C) in exon VIII of IXLA, with a predicted replacement of Ile-397 to Thr in the mature protein. This **mutation** is the same as found recently for IXLB. The observation that IXLB and IXLA have the same **mutation** is an unexpected finding, since, on the basis of their ox brain prothrombin time (PT, a test that measures the ability of the variant Factor IX molecules to **inhibit** the activation of Factor X by Factor VIIa-tissue factor complex), these variants have been classified into two different groups and were thought to be genetically different. Our observation thus suggests that the ox brain PT does not reflect the locus of **mutation** in the coding region of the variant molecules. However, our analysis suggests that the ox brain PT is related to Factor IX antigen concentration in the patient's plasma.

Importantly, although the **mutation** in IXLA or IXLB protein is in the catalytic domain, purified IXaLA and IXaLB hydrolyse L-tosylarginine methyl ester at rates very similar to that of normal IXa. These data, in conjunction with our recent data on Factor IXBm Lake Elsinore (Ala-390----Val mutant), strengthen a conclusion that the peptide region containing residues 390-397 of normal **Factor IXa** plays an essential role in macromolecular substrate catalysis and **inhibitor** binding. However, the two **mutations** noted thus far in this region do not distort S1 binding site in the **Factor IXa** enzyme.

L15 ANSWER 1 OF 29 CAPLUS COPYRIGHT 1999 ACS
AN 1999:245753 CAPLUS
DN 131:30148
TI Cleavage of factor V at arg 506 by activated protein C and the expression of anticoagulant activity of factor V
AU Thorelli, Elisabeth; Kaufman, Randal J.; Dahlback, Bjorn
CS Department of Clinical Chemistry, University Hospital Malmo, Lund University, Malmo, S-205 02, Swed.
SO Blood (1999), 93(8), 2552-2558
CODEN: BLOOAW; ISSN: 0006-4971
PB W. B. Saunders Co.
DT Journal
LA English

L15 ANSWER 2 OF 29 CAPLUS COPYRIGHT 1999 ACS
AN 1998:39035 CAPLUS
DN 128:178524
TI Blood coagulation factor IX residues Glu78 and Arg94 provide a link between both epidermal growth factor-like domains that is crucial in the interaction with factor VIII light chain
AU Christophe, Olivier D.; Lenting, Peter J.; Kolkman, Joost A.; Brownlee, George G.; Mertens, Koen
CS Dep. Plasma Protein Technol., Central Lab. Netherlands Red Cross Blood Transfusion Service, Amsterdam, Neth.
SO J. Biol. Chem. (1998), 273(1), 222-227
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English

L15 ANSWER 3 OF 29 CAPLUS COPYRIGHT 1999 ACS
AN 1998:34104 CAPLUS
DN 128:139327
TI The molecular basis for cross-reacting material-positive hemophilia A due to missense mutations within the A2-domain of factor VIII
AU Amano, Kagehiro; Sarkar, Rita; Pemberton, Susan; Kemball-Cook, Geoffrey; Kazazian, Haig H., Jr; Kaufman, Randal J.
CS The Howard Hughes Medical Institute and the Department of Biological Chemistry and University of Michigan Medical Center, Ann Arbor, MI, 48109-0650, USA
SO Blood (1998), 91(2), 538-548
CODEN: BLOOAW; ISSN: 0006-4971
PB W. B. Saunders Co.
DT Journal
LA English

L15 ANSWER 4 OF 29 CAPLUS COPYRIGHT 1999 ACS
AN 1997:710503 CAPLUS
DN 128:31607
TI Characterization of a genetically engineered inactivation-resistant coagulation factor VIIIa
AU Pipe, Steven W.; Kaufman, Randal J.
CS Department of Pediatrics, University of Michigan Medical Center, Ann Arbor, MI, 48109, USA
SO Proc. Natl. Acad. Sci. U. S. A. (1997), 94(22), 11851-11856
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English

L15 ANSWER 5 OF 29 CAPLUS COPYRIGHT 1999 ACS
AN 1997:621128 CAPLUS
DN 127:305789
TI Interaction of factor IXa with factor VIIIa. Effects of protease domain Ca2+ binding site, proteolysis in the autolysis loop, phospholipid, and factor X
AU Mathur, Akash; Zhong, Degang; Sabharwal, Arun K.; Smith, Kenneth J.; Bajaj, S. Paul
CS Departments of Medicine, Pathology, and Biochemistry, St. Louis University
School of Medicine, St. Louis, MO, 63104, USA
SO J. Biol. Chem. (1997), 272(37), 23418-23426
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English

L15 ANSWER 6 OF 29 CAPLUS COPYRIGHT 1999 ACS
AN 1996:623402 CAPLUS
DN 125:295894
TI Ca2+ binding to the first epidermal growth factor-like domain of human blood coagulation factor IX promotes enzyme activity and factor VIII light
chain binding
AU Lenting, Peter J.; Christophe, Olivier D.; ter Maat, Hans; Rees, D. Jasper
G.; Mertens, Koen
CS Dep. Plasma Protein Technol., Central Lab. Netherlands Red Cross Blood Transfusion Service, Amsterdam, 1066 CX, Neth.
SO J. Biol. Chem. (1996), 271(41), 25332-25337
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English

L15 ANSWER 7 OF 29 CAPLUS COPYRIGHT 1999 ACS
AN 1995:984661 CAPLUS
DN 124:311018
TI Functional consequences of the Ser334.fwdarw.Pro mutation in a human factor X variant (factor XMarseille)
AU Bezeaud, Annie; Miyata, Toshiyuki; Helley, Dominique; Zeng, Yan-Zhen; Kato, Hisao; Aillaud, Marie-Francoise; Juhan-Vague, Irene; Guillin, Marie-Claude
CS Faculte Xavier Bichat, Laboratoire de Recherche sur l'Hemostase et la Thrombose, Paris, F-75870, Fr.
SO Eur. J. Biochem. (1995), 234(1), 140-7
CODEN: EJBCAI; ISSN: 0014-2956
DT Journal
LA English

L15 ANSWER 8 OF 29 CAPLUS COPYRIGHT 1999 ACS
AN 1995:874542 CAPLUS
DN 123:279673
TI X-ray structure of clotting factor IXa: active site and module structure related to Xase activity and hemophilia B
AU Brandstetter, Hans; Bauer, Margit; Huber, Robert; Lollar, Pete; Bode, Wolfram
CS Max-Planck-Inst. Biochem., Martinsried, D82152, Germany
SO Proc. Natl. Acad. Sci. U. S. A. (1995), 92(21), 9796-800
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English

L15 ANSWER 9 OF 29 CAPLUS COPYRIGHT 1999 ACS
AN 1995:857995 CAPLUS
DN 123:311090

TI Enhanced plasmin inhibition by a reactive center lysine mutant of the Kunitz-type protease inhibitor domain of the amyloid .beta.-protein precursor
AU Van Nostrand, William E.; Schmaier, Alvin H.; Siegel, Robert S.; Wagner, Steven L.; Raschke, William C.
CS Dep. Microbiol. Mol. Genet., Univ. California, Irvine, CA, 92717-4025, USA
SO J. Biol. Chem. (1995), 270(39), 22827-30
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English

L15 ANSWER 10 OF 29 CAPLUS COPYRIGHT 1999 ACS
AN 1995:531367 CAPLUS
DN 123:4305
TI Kinetic characterization of the proteinase binding defect in a reactive site variant of the serpin, antithrombin. Role of the P1' residue in transition-state stabilization of antithrombin-proteinase complex formation
AU Olson, Steven T.; Stephens, Andrew W.; Hirs, C. H. W.; Bock, Paul E.; Bjoerk, Ingemar
CS Center Molecular Biology Oral Diseases, University Illinois-Chicago, Chicago, IL, 60612, USA
SO J. Biol. Chem. (1995), 270(17), 9717-24
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English

L15 ANSWER 11 OF 29 CAPLUS COPYRIGHT 1999 ACS
AN 1995:79009 CAPLUS
DN 122:126555
TI The role of amino-terminal residues of the heavy chain of factor IXa in the binding of its cofactor, factor VIIIa
AU Hamaguchi, Nobuko; Bajaj, S. Paul; Smith, Kenneth J.; Stafford, Darrel W.
CS Med. Cent., Duke Univ., Durham, NC, USA
SO Blood (1994), 84(6), 1837-42
CODEN: BLOOAW; ISSN: 0006-4971
DT Journal
LA English

L15 ANSWER 12 OF 29 CAPLUS COPYRIGHT 1999 ACS
AN 1994:505112 CAPLUS
DN 121:105112
TI Factor V and protein S as synergistic cofactors to activated protein C in degradation of factor VIIIa
AU Shen, Lei; Dahlbaeck, Bjoern
CS Dep. Clin. Chem., Univ. Lund, Malmoe, S-21401, Swed.
SO J. Biol. Chem. (1994), 269(29), 18735-8
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English

L15 ANSWER 13 OF 29 CAPLUS COPYRIGHT 1999 ACS
AN 1992:233063 CAPLUS
DN 116:233063
TI Hemophilia B caused by five different nondeletion mutations in the protease domain of factor IX
AU Ludwig, M.; Sabharwal, A. K.; Brackmann, H. H.; Olek, K.; Smith, K. J.; Birktoft, J. J.; Bajaj, S. P.
CS Inst. Exp. Haematol. Blood Transfus., Bonn, Germany
SO Blood (1992), 79(5), 1225-32
CODEN: BLOOAW; ISSN: 0006-4971
DT Journal
LA English

L15 ANSWER 14 OF 29 CAPLUS COPYRIGHT 1999 ACS

AN 1990:530050 CAPLUS
DN 113:130050
TI Mutations in hemophilia Bm occur at the Arg180-Val activation site or in the catalytic domain of factor IX
AU Bertina, Rogier M.; Van der Linden, Irma K.; Mannucci, Pierro M.; Reinalda-Poot, Hanneke H.; Cupers, Rosemiek; Poort, Swibertus R.; Reitsma, Pieter H.
CS Haemostasis Thromb. Res. Unit, Univ. Hosp., Leiden, 2300 RC, Neth.
SO J. Biol. Chem. (1990), 265(19), 10876-83
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English

L15 ANSWER 15 OF 29 CAPLUS COPYRIGHT 1999 ACS
AN 1990:176354 CAPLUS
DN 112:176354
TI Experimental and theoretical evidence supporting the role of Gly363 in blood coagulation factor IXa (Gly193 in chymotrypsin) for proper activation of the proenzyme
AU Bajaj, S. Paul; Spitzer, Silvia G.; Welsh, William J.; Warn-Cramer, Bonnie J.; Kasper, Carol K.; Birktoft, Jens J.
CS Sch. Med., St. Louis Univ., St. Louis, MO, 63104, USA
SO J. Biol. Chem. (1990), 265(5), 2956-61
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English

L15 ANSWER 16 OF 29 CAPLUS COPYRIGHT 1999 ACS
AN 1990:154207 CAPLUS
DN 112:154207
TI Synthesis, purification, and characterization of an Arg152 .fwdarw. Glu site-directed mutant of recombinant human blood clotting factor VII
AU Wildgoose, Peter; Berkner, Kathleen L.; Kisiel, Walter
CS Sch. Med., Univ. New Mexico, Albuquerque, NM, 87131, USA
SO Biochemistry (1990), 29(13), 3413-20
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English

L15 ANSWER 17 OF 29 CAPLUS COPYRIGHT 1999 ACS
AN 1990:96115 CAPLUS
DN 112:96115
TI Replacement of isoleucine-397 by threonine in the clotting proteinase Factor IXa (Los Angeles and Long Beach variants) affects macromolecular catalysis but not L-tosylarginine methyl ester hydrolysis. Lack of correlation between the ox brain prothrombin time and the mutation site in the variant proteins
AU Spitzer, Silvia G.; Warn-Cramer, Bonnie J.; Kasper, Carol K.; Bajaj, S. Paul
CS Sch. Med., St. Louis Univ., St. Louis, MO, 63104, USA
SO Biochem. J. (1990), 265(1), 219-25
CODEN: BIJOAK; ISSN: 0306-3275
DT Journal
LA English

L15 ANSWER 18 OF 29 EUROPATFULL COPYRIGHT 1999 WILA

PATENT APPLICATION - PATENTANMELDUNG - DEMANDE DE BREVET

AN 859058 EUROPATFULL ED 19980830 EW 199834 FS OS
TIEN Nucleic acid construct for expression of protease activatable substances.

TIDE Nukleinsaeurekonstrukt zur Expression von durch Proteasen aktivierbaren Wirksubstanzen, sowie Herstellung und Verwendung.
TIFR Produit d'acide nucleique pour l'expression de substances activable par protease.
IN Heidtmann, Hans Heinrich, Dr., Bogenstrasse 8, 27568 Bremerhahven, DE; Mueller, Rolf, Prof. Dr., Poitiersstrasse 8, 35037 Marburg, DE; Sedlacek, Hans-Harald, Prof. Dr., Sonnenhang 3, 35041 Marburg, DE
PA HOECHST AKTIENGESELLSCHAFT, Brueningstrasse 50, 65929 Frankfurt am Main, DE
SO Wila-EPZ-1998-H34-T1a
DS R AT; R BE; R CH; R DE; R DK; R ES; R FI; R FR; R GB; R GR; R IE; R IT; R LI; R LU; R MC; R NL; R PT; R SE
PIT EPA2 EUROPAEISCHE PATENTANMELDUNG
PI EP 859058 A2 19980819
OD 19980819
AI EP 1998-100632 19980115
PRAI DE 1997-19701141 19970116
IC ICM C12N015-85
ICS C12N015-12 C12N015-52 C12N009-00 C12N009-64
C07K014-47 A61K048-00

L15 ANSWER 19 OF 29 EUROPATFULL COPYRIGHT 1999 WILA

PATENT APPLICATION - PATENTANMELDUNG - DEMANDE DE BREVET

AN 776980 EUROPATFULL ED 19970622 EW 199723 FS OS
TIEN Evaluation of substances for altering and for increasing APC response.
TIDE Verfahren zur Bewertung von Substanzen zum Steigen bzw. zur Modifizierung der APC-Aktivitaet.
TIFR L'evaluation de substances pour augmenter et pour modifier l'activite pour l'APC.
IN Rosing, Jan, Dr., Prinses Beatrixsingel 15, 6301 VK Valkenburg, NL; Tans, Guido, Dr., Pallashof 29, 6215 XK Maastricht, NL; Varadi, Katalin, Dr., Othellogasse 1/6/2, 1230 Vienna, AT; Schwarz, Hans-Peter, Doz., Schindlergasse 32, 1180 Vienna, AT
PA IMMUNO AG, Industriestrasse 67, 1221 Wien, AT
SO Wila-EPZ-1997-H23-T1a
DS R AT; R BE; R CH; R DE; R DK; R ES; R FI; R FR; R GB; R IT; R LI; R NL; R SE
PIT EPA1 EUROPAEISCHE PATENTANMELDUNG
PI EP 776980 A1 19970604
OD 19970604
AI EP 1996-117704 19961105
PRAI US 1995-555423 19951109
IC ICM C12Q001-56
ICS A61K038-36 G01N033-86

L15 ANSWER 20 OF 29 EUROPATFULL COPYRIGHT 1999 WILA

PATENT APPLICATION - PATENTANMELDUNG - DEMANDE DE BREVET

AN 718628 EUROPATFULL UP 19970408 EW 199626 FS OS STA R
TIEN Method for diagnosis of blood coagulation disorders.
TIDE Verfahren zur Diagnose von Blutgerinnungsstoerungen.
TIFR Procede de diagnostic de desordres de la coagulation du sang.
IN Denson, Kenneth William Ernest, Two Chestnuts, Emmington, Oxon OX9 4AA, GB
PA Diagnostic Reagents Limited, Wenman Road, Thame, Oxon OX9 3NY, GB
SO Wila-EPZ-1996-H26-T2a
DS R AT; R BE; R CH; R DE; R DK; R ES; R FR; R GB; R GR; R IE; R IT; R LI; R LU; R MC; R NL; R PT; R SE
PIT EPA1 EUROPAEISCHE PATENTANMELDUNG
PI EP 718628 A1 19960626
OD 19960626
AI EP 1995-304016 19950609

PRAI EP 1994-309764 19941223
IC ICM G01N033-86
ICS C12Q001-56

L15 ANSWER 21 OF 29 EUROPATFULL COPYRIGHT 1999 WILA

GRANTED PATENT - ERTEILTES PATENT - BREVET DELIVRE

AN 703923 EUROPATFULL ED 19981018 EW 199841 FS PS
TIEN FACTOR VII-DERIVED PEPTIDES.
TIDE FAKTOR VII-PEPTIDE.
TIFR PEPTIDES DERIVES DU FACTEUR VII.
IN STEPHENS, Ross Wentworth, Silurveien 19, N-0380 Oslo, NO;
ORNING, Lars, Thomas Heftyes gate 47B, N-0267 Oslo, NO;
SAKARIASSEN, Kjell Steinar, Kygd Alle 33B, N-0262 Oslo, NO
PA NYCOMED IMAGING AS, Nycoveien 1-2, 0401 Oslo 4, NO
SO Wila-EPS-1998-H41-T1
DS R AT; R BE; R CH; R DE; R DK; R ES; R FR; R GB; R GR; R IE; R IT; R LI;
R LU; R MC; R NL; R PT; R SE
PIT EPB1 EUROPAEISCHE PATENTSCHRIFT (Internationale Anmeldung)
PI EP 703923 B1 19981007
OD 19960403
AI EP 1994-918437 19940617
PRAI GB 1993-12601 19930618
GB 1994-9335 19940510
RLI WO 94-GB1315 940617 INTAKZ
WO 9500541 950105 INTPNR
REP EP 446797 A WO 90-03390 A
WO 93-09804 A
IC ICM C07K007-06
ICS A61K038-08

L15 ANSWER 22 OF 29 EUROPATFULL COPYRIGHT 1999 WILA

GRANTED PATENT - ERTEILTES PATENT - BREVET DELIVRE

AN 690991 EUROPATFULL ED 19980802 EW 199830 FS PS
TIEN NOVEL ANTICOAGULANT COFACTOR ACTIVITY.
TIDE NEUE ANTIKOAGULANT-COFAKTOR AKTIVITAeT.
TIFR NOUVELLE ACTIVITE DE COFACTEUR ANTICOAGULANT.
IN DAHLBAeCK, Bjoern, Plantskolevaegen 10, S-216 21 Malmoe, SE
PA DAHLBAeCK, Bjoern, Plantskolevaegen 10, S-216 21 Malmoe, SE
SO Wila-EPS-1998-H30-T2
DS R AT; R BE; R CH; R DE; R DK; R ES; R FR; R GB; R GR; R IE; R IT; R LI;
R LU; R MC; R NL; R PT; R SE
PIT EPB1 EUROPAEISCHE PATENTSCHRIFT (Internationale Anmeldung)
PI EP 690991 B1 19980722
OD 19960110
AI EP 1994-905908 19940128
PRAI SE 1993-300 19930129
SE 1993-2457 19930720
RLI WO 94-SE70 940128 INTAKZ
WO 9417415 940804 INTPNR
REP EP 434377 A EP 608235 A
WO 91-02812 A
REN Dialog Information Services, file 155, Medline, Dialog Acc. No. 06816150, VUKOVICH T. et al.: "Replacement Therapy for a Homozyqous Protein C Deficiency-State Using a Concentrate of Human Protein C and S", Br. J. Haematol. (England), Dec. 1988, 70 (4), p435-40. Dialog Information Services, file 155, Medline, Dialog Acc. No. 04395705, KATZMANN J.A. et al.: "Isolation of Functional Human Coagulation Factor V by Using a Hybridoma Antibody", Proc. Natl. Acad. Sci. USA (United States), Jan. 1981, 78 (1), p162-6. Dialog Information Services, file 155, Medline, Dialog Acc. No. 05862119, CORNILLON B. et al.: "Rat Coagulation Factor V Purification and Production of the Monospecific Antiserum", Comp. Biochem. Physiol. (England), 1986, 83 (2), p397-401

IC ICM G01N033-86
ICS C12Q001-56 C07K014-745 A61K038-36

L15 ANSWER 23 OF 29 EUROPATFULL COPYRIGHT 1999 WILA

GRANTED PATENT - ERTEILTES PATENT - BREVET DELIVRE

AN 642352 EUROPATFULL ED 19990204 EW 199903 FS PS
TIEN TRUNCATED TISSUE FACTOR AND FVIIA OR FVII ACTIVATOR FOR BLOOD COAGULATION.
TIDE VERKUeRZTER GEWEBSFAKTOR UND FVIIA ODER FVII ZUR AKTIVIERUNG DER BLUTGERINNUNG.
TIFR TRAITEMENT DES HEMORRAGIES AU MOYEN DU FACTEUR TISSULAIRE MODIFIE EN COMBINAISON AVEC UN ACTIVATEUR DU FACTEUR VIIA OU VII.
IN MORRISSEY, James, H., 228 W. Eubanks, Oklahoma City, OK 73118, US; COMP, Philip, C., 9805 Silver Lake Drive, Oklahoma City, OK 73118, US
PA Oklahoma Medical Research Foundation, 825 N.E. 13th Street, Oklahoma City Oklahoma 73104, US
SO Wila-EPS-1999-H03-T1
DS R AT; R BE; R CH; R DE; R DK; R ES; R FR; R GB; R IE; R IT; R LI; R NL; R SE
PIT EPB1 EUROPAEISCHE PATENTSCHRIFT (Internationale Anmeldung)
PI EP 642352 B1 19990120
OD 19950315
AI EP 1993-913844 19930512
PRAI US 1992-882202 19920513
US 1993-21615 19930219
RLI WO 93-US4493 930512 INTAKZ
WO 9323074 931125 INTPNR
REP EP 225160 A
REN JOURNAL OF BIOLOGICAL CHEMISTRY. vol. 266, no. 4, 5 February 1991, BALTIMORE US pages 2158 - 2166 W. RUF ET AL. 'PHOSPHOLIPID-INDEPENDENT AND -DEPENDENT INTERACTIONS REQUIRED FOR TISSUE FACTOR RECEPTOR AND COFACTOR FUNCTION.' cited in the application FASEB JOURNAL vol. 6, no. 1, 1 January 1992, BETHESDA, MD US page A330 R.C. HAPAK ET AL. 'THE LOCATION OF THE ACTIVE SITE OF FACTOR VIIa ABOVE THE MEMBRANE SURFACE
IS
ALTERED BY EITHER FULL-LENGHT OR TRUNCATED TISSUE FACTOR.' CHEMICAL ABSTRACTS, vol. 109, no. 17, 24 October 1988, Columbus, Ohio, US; abstract no. 142300r, A.R. GILES ET AL. 'A COMBINATION OF FACTOR Xa AND PHOSPHATIDYLCHOLINE-PHOSPHATIDYLSERINE VESICLES BYPASSES FACTOR VIII IN VIVO.' page 42;
IC ICM A61K038-48
ICI A61K038-48 A61K038:00

L15 ANSWER 24 OF 29 EUROPATFULL COPYRIGHT 1999 WILA

GRANTED PATENT - ERTEILTES PATENT - BREVET DELIVRE

AN 567636 EUROPATFULL ED 19970307 EW 199702 FS PS
TIEN PROTEIN S ASSAY.
TIDE BESTIMMUNGSVERFAHREN FUeR PROTEIN S.
TIFR DOSAGE DE LA PROTEINE S.
IN VAN DE WAART, Piet, Kurmat Strasse 23, CH-3184 Wuennewil, CH; WOODHAMS, Barry, J., Route de Tavel 9, CH-1700 Fribourg, CH
PA Dade Produktions AG, Bonnstrasse, 3186 Duedingen, CH
SO Wila-EPS-1997-H02-T1
DS R AT; R BE; R CH; R DE; R DK; R ES; R FR; R GB; R IE; R IT; R LI; R NL; R SE
PIT EPB1 EUROPAEISCHE PATENTSCHRIFT (Internationale Anmeldung)
PI EP 567636 B1 19970108
OD 19931103
AI EP 1992-925327 19921120
PRAI US 1991-796032 19911120
RLI WO 92-US9971 921120 INTAKZ
WO 9310262 930527 INTPNR

REP EP 236985 A EP 445626 A
WO 91-01382 A
REN THROMBOSIS RESEARCH, vol. 49, no. 2, 15 January 1988, New York, NY (US);
K. SUZUKI et al., pp. 241-251 THROMBOSIS RESEARCH, vol. 60, no. 1, 01 October 1990, New York, NY (US); L. PREDA et al. pp 19-32 JOURNAL OF LABORATORY & CLINICAL MEDICINE, vol. 115, no. 4, April 1990, St. Louis, MO (US); M.E. RICK et al., pp. 415-421 THROMBOSIS RESEARCH, vol. 10, no.
2, 1977, New York, NY (US); H. SUOMELA et al., pp. 267-281 RESEARCH IN CLINICAL LABORATORY, vol. 20, 1990; R.M. BERTINA, pp. 127-138 DATABASE WPIL, sect. Ch, week 8914, Derwent Publications Ltd., London (GB); class
B04, acc. no. 89103936 ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE, vol.
112, no. 1, January 1988, Chicago, IL (US); K.A. HIGH, pp. 28-36
IC ICM C12Q001-56
ICS G01N033-86

L15 ANSWER 25 OF 29 EUROPATFULL COPYRIGHT 1999 WILA

GRANTED PATENT - ERTEILTES PATENT - BREVET DELIVRE

AN 521873 EUROPATFULL ED 19990613 EW 199922 FS PS
TIEN ANTICOAGULANT PROTEINS.
TIDE ANTIKOAGULIERENDE PROTEINE.
TIFR PROTEINES ANTICOAGULANTES.
IN BERKNER, Kathleen, L., 3032 - 22nd Avenue West, Seattle, WA 98199, US
PA ZYMOGENETICS, INC., 4225 Roosevelt Way N.E., Seattle, WA 98108, US
SO Wila-EPS-1999-H22-T1
DS R AT; R BE; R CH; R DE; R DK; R ES; R FR; R GB; R GR; R IT; R LI; R LU; R NL; R SE
PIT EPB1 EUROPAEISCHE PATENTSCHRIFT (Internationale Anmeldung)
PI EP 521873 B1 19990602
OD 19930113
AI EP 1991-904449 19910125
PRAI US 1990-471313 19900129
RLI WO 91-US552 910125 INTAKZ
WO 9111514 910808 INTPNR
REP US 4784950 A
REN BIOCHEMISTRY, vol. 29, no. 13, 3 April 1990, EASTON, PA US, pages 3413-3420; P. WILDGOOSE ET AL: 'Synthesis, purification and characterization of an recombinant human blood clotting factor VII' Proceedings of the National Academy of Science, USA, Vol. 83, issued April 1986, HAGEN et al., "Characterization of a cDNA coding for human factor VIII", pages 2412-2416, see whole publication. Proceedings of the
National Academy of Science, USA, Vol. 85, issued April 1988, PITTMAN et
al., "Proleoytic requirement for thrombin activation of anti-hemophilic factor (factor VIII)" pages 2429-2433, see whole publication, especially
the Abstract
IC ICM C12N015-57
ICS C12N009-64 A61K038-36 C12N005-10

L15 ANSWER 26 OF 29 EUROPATFULL COPYRIGHT 1999 WILA

GRANTED PATENT - ERTEILTES PATENT - BREVET DELIVRE

AN 502968 EUROPATFULL ED 19970806 EW 199730 FS PS
TIEN ACTIVATABLE FIBRINOLYTIC AND ANTI-THROMBOTIC PROTEINS.
TIDE AKTIVIERBARE FIBRINOLYTISCHE UND ANTITHROMBOTISCHE PROTEINE.
TIFR PROTEINES FIBRINOLYTIQUES ET ANTITHROMBOTIQUES ACTIVABLES.
IN DAWSON, Keith Martyn, 80 Barnards Hill, Marlow, Bucks SL7 2NZ, GB;
EDWARDS, Richard Mark, 7 Ludlow Drive, Thame, Oxon OX9 3XS, GB;

FORMAN, Joan Mabel, 6 Margaret Road, Oxford OX3 8NG, GB
PA BRITISH BIOTECH PHARMACEUTICALS LIMITED, Watlington Road, Cowley Oxford,
OX4 5LY, GB
SO Wila-EPS-1997-H30-T1
DS R AT; R BE; R CH; R DE; R DK; R ES; R FR; R GB; R GR; R IT; R LI; R LU; R NL; R SE
PIT EPB1 EUROPAEISCHE PATENTSCHRIFT (Internationale Anmeldung)
PI EP 502968 B1 19970723
OD 19920916
AI EP 1991-900851 19901207
PRAI GB 1989-27722 19891207
RLI WO 90-GB1912 901207 INTAKZ
WO 9109118 910627 INTPNR
REP EP 211299 A EP 227938 A
EP 292009 A EP 297882 A
EP 304013 A EP 319944 A
EP 323149 A EP 330700 A
EP 338841 A WO 89-01036 A
WO 89-06239 A WO 90-10081 A
WO 90-13640 A WO 91-08297 A
REN Biochemistry, vol. 29, 1990, American Chemical Society, D.J. Davidson et
al.: "plasminogen activator activities of equimolar complexes of streptokinase with variant recombinant plasminogens", pages 3585-3590 Chemical Abstracts, vol. 103, 1985, (Columbus, Ohio, US); J.Y. Chang: "Thrombin specificity. Requirement for apolar amino acids adjacent to the thrombin cleavage site of polypeptiede substrate", see page 412 Archives of Biochemistry and Biophysics, vol. 271, no. 2, June 1989, Academic Press, Inc.; J. Whitefllet-Smith et al.: "Expression of human plasminogen cDNA in a baculovirus vector-infected insect cell system", pages 390-399 Proc. Natl. Acad. Sci. USA, vol. 79, October 1982; T. Miyata et al.: "Plasminogen Tochigi: inactive plasmin resulting from replacement of alanine- 600 by threonine in the active site", pages 6132-6136
IC ICM C12N009-68
ICS C12N015-57 A61K038-48

L15 ANSWER 27 OF 29 EUROPATFULL COPYRIGHT 1999 WILA

GRANTED PATENT - ERTEILTES PATENT - BREVET DELIVRE

AN 443874 EUROPATFULL ED 19970604 EW 199720 FS PS
TIEN Vectors and compounds for expression of glycosylation mutants of human protein C.
TIDE Vektoren und Zusammensetzungen zur Expression von Glykosilationsmutanten
des menschlichen Proteins-C.
TIFR Vecteurs et composes pour l'expression de mutantes de glycosylation de proteine C humaine.
IN Gerlitz, Bruce Edward, 5551 Vicksburg Drive, Indianapolis, Indiana 46254, US;
Grinnell, Brian William, 3625 East 71st Street, Indianapolis, Indiana 46220, US
PA ELI LILLY AND COMPANY, Lilly Corporate Center, Indianapolis, Indiana 46285, US
SO Wila-EPS-1997-H20-T1
DS R AT; R BE; R CH; R DE; R DK; R ES; R FR; R GB; R GR; R IT; R LI; R LU; R NL; R SE
PIT EPB1 EUROPAEISCHE PATENTSCHRIFT
PI EP 443874 B1 19970514
OD 19910828
AI EP 1991-301446 19910222
PRAI US 1990-484081 19900223
US 1990-628063 19901221
REP EP 191606 A EP 319312 A

EP 323149 A EP 352651 A
IC ICM C12N015-12
ICS C07H021-04 C12N015-63 C12N005-10

L15 ANSWER 28 OF 29 EUROPATFULL COPYRIGHT 1999 WILA

GRANTED PATENT - ERTEILTES PATENT - BREVET DELIVRE

AN 419099 EUROPATFULL ED 19970108 EW 199606 FS PS
TIEN Proteins having anticoagulant properties.
TIDE Proteine mit antikoagulierenden Eigenschaften.
TIFR Proteines ayant des proprietes anticoagulantes.
IN Vlasuk, George P., 786 Hartley Drive, Lansdale, PA 19446, US;
Waxman, Lloyd H., RR1 Box 146C Byers Road, Ottsville, PA 18942, US;
Garsky, Victor M., 752 Palmer Place, Blue Bell, PA 19442, US;
Neeper, Michael P., 1001 Townsend Cr., Wayner, PA 19087, US
PA MERCK & CO. INC., 126, East Lincoln Avenue P.O. Box 2000, Rahway New Jersey 07065-0900, US
SO Wila-EPS-1996-H06-T1
DS R AT; R BE; R CH; R DE; R DK; R ES; R FR; R GB; R IT; R LI; R LU; R NL; R SE
PIT EPB1 EUROPAEISCHE PATENTSCHRIFT
PI EP 419099 B1 19960207
OD 19910327
AI EP 1990-309834 19900907
PRAI US 1989-404033 19890907
US 1990-498307 19900323
US 1990-565164 19900813
REN THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 265, no. 29, 15th October 1990, pages 17746-17752; M.P. NEEPER et al.: "Characterization of recombinant tick anticoagulant peptide" SCIENCE, vol. 248, 4th May 1990,
pages 593-596; L. WAXMAN et al.: "Tick anticoagulant peptide (TAP) is a novel inhibitor of blood coagulation factor Xa"
IC ICM C07K014-81
ICS A61K038-55

L15 ANSWER 29 OF 29 USPATFULL
AN 1998:146183 USPATFULL
TI Method for inhibiting thrombosis in a patient whose blood is subjected to extracorporeal circulation
IN Rose, Eric, Tenafly, NJ, United States
Stern, David, Great Neck, NY, United States
Schmidt, Ann Marie, Franklin Lakes, NJ, United States
Spanier, Talia, New York, NY, United States
PA The Trustees of Columbia University in the City of New York, New York, NY, United States (U.S. corporation)
PI US 5839443 19981124
AI US 1996-648561 19960516 (8)
DT Utility
LN.CNT 940
INCL INCLM: 128/898.000
INCLS: 435/013.000
NCL NCLM: 128/898.000
NCLS: 435/013.000
IC [6]
ICM: A61B019-00
EXF 128/898; 530/384; 436/69; 435/183; 435/13; 604/49